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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No. 1398-002
First Inventor or Application Identifier Alfred T. Sapse, M.D.
Title COMPOSITION OF ANTI-HIV DRUGS AND ...
Express Mail Label No. EL039911232US

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

1. ☒ Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
2. ☒ Specification (Total Pages 27)
(preferred arrangement set forth below)
- Descriptive title of the invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to Microfiche Appendix
 - Background of the invention
 - Brief Summary of the invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure

3. ☐ Drawing(s) (35 U.S.C. 113) (Total Sheets ☐)

4. Oath or Declaration (Total Pages 3)

- a. ☒ Newly executed (original or copy)
- b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 17 completed)
(Note Box 5 below)
- i. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

5. ☐ Incorporation By Reference (useable if Box 4b is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein

6. ☐ Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
- a. ☐ Computer Readable Copy
 - b. ☐ Paper Copy (identical to computer copy)
 - c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☒ Assignment Papers (cover sheet & document(s))
9. ☐ 37 C.F.R. § 3.73(b) Statement (when there is an assignee) ☐ Power of Attorney
10. ☐ English Translation Document (if applicable)
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
- * Small Entity ☐ Statement filed in prior application, Status still proper and desired
14. ☒ Statement(s) (PTO/SB/09-12)
15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)
16. ☐ Other

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17. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. _____

Prior application information: Examiner _____ Group / Art Unit _____

18. CORRESPONDENCE ADDRESS

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Applicant: Dr. Alfred T. Sapse, M.D.
Docket No.: 1398-002
Serial No.: _____
Filed: January 21, 1999
For: Composition of Anti-HIV and Anti-Cortisol Compounds
Decreasing The Side Effects of Anti-HIV Drugs In A
Human

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY
STATUS (37 CFR 1.27(a)) - SMALL BUSINESS CONCERN**

I hereby declare that I am

- ☐ the owner of the small business concern identified below:
☒ an official of the small business concern empowered to act on behalf of the concern
identified below:

NAME OF CONCERN: Steroidogenesis Inhibitors, Inc.
ADDRESS OF CONCERN: 2001 East Flamingo Rd., Suite B, Las Vegas, Nevada 89119

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract of law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled COMPOSITION OF ANTI-HIV AND ANTI-CORTISOL COMPOUNDS DECREASING THE SIDE EFFECTS OF ANTI-HIV DRUGS IN A HUMAN inventor Alfred T. Sapse, M.D. in:

- ☒ the specification filed herewith
☐ application Serial No. _____ filed _____

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statement are required from each person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME _____

ADDRESS _____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate (37 CFR 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements are made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING _____

Dr. Alfred T. Sapse, M.D.
Dr. Alfred T. Sapse, M.D., President

ADDRESS OF PERSON SIGNING _____

Steroidogenesis Inhibitors, Inc., 2001 East Flamingo Rd., Suite B,
Las Vegas, Nevada 89119

SIGNATURE _____

Asay DATE 1/21/99

Express Mail Number: EL039911232US

Date of Deposit: January 21, 1999

APPLICATION FOR UNITED STATES LETTERS PATENT

FOR

COMPOSITION OF ANTI-HIV DRUGS AND ANTI-CORTISOL COMPOUNDS AND
METHOD FOR DECREASING THE SIDE EFFECTS OF ANTI-HIV DRUGS IN A HUMAN

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COMPOSITION OF ANTI-HIV DRUGS AND ANTI-CORTISOL COMPOUNDS AND METHOD FOR DECREASING THE SIDE EFFECTS OF ANTI-HIV DRUGS IN A HUMAN

Inventor: Alfred T. Sapse, M.D.

Technical Field

The present invention relates generally to a composition for oral (enteral) administration
5 to an individual infected with human immunodeficiency virus (HIV) and to a method for
decreasing the side effects of anti-HIV drug therapy. More specifically, the present invention
relates to a composition which comprises at least one anti-HIV drug and at least one anti-cortisol
or (cortisol blocker) compound. The method of the present invention comprises administering to
a human that is receiving anti-HIV drugs a composition comprising at least one anti-cortisol
10 compound.

Background of the Invention

Cortisol, also known as hydrocortisone, is a glucocorticoid of the adrenal cortex that is a
derivative of cortisone . At normal physiological levels (2-25 mg/dl) cortisol is a naturally
15 occurring anti-inflammatory steroid. However, when cortisol is present in the blood at elevated
levels, above about 30 mg/dl, it acts as a catabolic stress hormone, cannibalizes muscle tissue and
can destroy practically every cell, tissue and organ in the human body. For example, high
cortisol levels can result in the breakdown of connective tissue, lowered immunity, reduced
muscle RNA synthesis, redistribution of fat and other maladies. In the human immune system
20 elevated levels of cortisol can induce a lowering of the number of CD₄ cells, elevation of CD₈

cell levels, and disappearance of natural killer cells. These are symptoms often found in HIV and AIDS patients.

Elevated cortisol levels are found in many diseases, including aging related conditions and depression. While it was initially thought that elevated cortisol was the result of these diseases, there is now evidence that high cortisol levels actually play a role in causing these diseases. As such, it had been suggested that tracking and treating increased levels of cortisol could be used to treat or prevent high cortisol diseases such as cancer, ulcers, myocardial infarction, diabetes, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), strokes, psoriasis, Alzheimer's disease, Space Adaption Syndrome, and the like, where elevated cortisol is constantly found.

Blood serum cortisol levels are considered "normal" if the 2-25 mg/dl range, with 7-25 mg/dl being normal for the morning hours (8:00 am), and 2-9 mg/dl being normal for the afternoon hours (5:00 pm).

In order to reduce the effects of prolonged high cortisol levels, a cortisol antagonist or cortisol blocker or anti-cortisol compound would be beneficial to the patient. Even more beneficial to the patient would be a mixture of cortisol antagonists that act synergistically. As used herein and in the claims, the term "cortisol blocker" means any known chemical entity or combination of entities that, when administered to an individual, will retard or prevent the production of cortisol or inhibit or prevent the catabolic activity of cortisol. Specific examples of cortisol blockers include RU 486, DHEA, ketoconazole, procaine hydrochloride, zinc and salts of zinc, ascorbic acid, Ipriflavone, HMB phosphatidylserine and others as more fully described below. An aspect of the present invention is directed to the use of at least one, preferably a

combination of cortisol antagonists in combination with anti-HIV drugs, to minimize the side effects of the anti-HIV drug therapy.

Drug treatment for human immunodeficiency virus (HIV), the etiologic agent of the acquired immunodeficiency syndrome (AIDS) and AIDS related complex includes

5 azidothymidine (3'-azido-3'-deoxythymidine; zidovudine (Retrovir)) or AZT. While clinical benefits against AIDS have been reported, serious adverse reactions, particularly bone marrow suppression, have been observed. In a study of the toxicity of AZT in the treatment of AIDS patients, nausea, myalgia, insomnia, Cushings like symptoms and severe headaches have been reported by recipients of AZT when compared to those on placebo. Anemia typically develops
10 in 24% of AZT recipients often requiring multiple red blood cell transfusions.

It has also been reported that people taking combination or "cocktail" drug treatments for HIV infection, develop bizarre symptoms that evidence dangerous disruption of the patient's lipid metabolism. Symptoms such as loss of subdermal fat for most of the body, development of hardened fat deposits in the stomachs and on the necks, elevations in triglycerides and
15 cholesterol, and insulin intolerance have been reported. The "buffalo humps" and "protease paunches" appear to be disruptions of fat metabolism caused by the use of drugs for the treatment of HIV infections.

The fat metabolism side effects have been directly linked to four (4) anti-HIV drugs called protease inhibitors. Those protease inhibitors include Indinavir, Viracept, Ritonavir and
20 Saquinavir. A consequence of an imbalance in fat metabolism is akin to Cushing's like disease or Cushingoid manifestations. Other side effects associated with these anti-HIV drugs include changes akin to a pre-diabetes state. Triglycerides and higher cholesterol levels have also been

reported. While not actually Cushing's disease, which is a high cholesterol disorder that causes similar "buffalo humps", the actual mechanism for the observed side effects of the anti-HIV drugs is not understood.

It is not unusual for HIV infected individuals to receive a number of cocktail of the anti-HIV drugs, also known as anti-HIV cocktails. Some investigators have speculated that the association between the administration of the anti-HIV cocktails and the development of the Cushingoid-like symptoms suggests that the anti-HIV drugs are likely responsible for the fat redistribution in the patients.

Background Art

U.S. Patent No. 4,956,391 to Sapse discloses a composition for the treatment of individuals addicted to narcotics. The composition comprises procaine and a complexing agent capable of forming a protected complex with procaine. The complexing agent is disclosed as an acid such as ascorbic acid, pantothenic acid, acetylsalicylic acid and amino acids. A preferred combination useful in the present invention is the stabilized procaine hydrochloride (procaine HCl) according to U.S. Patent 4,956,391. Thus, the teachings of U.S. Patent 4,956,391 are useful in understanding certain embodiments of the present invention. This patent does not disclose nor suggest the preferred combination of this invention which comprises procaine, ascorbic acid (vitamin C) and a zinc salt such as zinc heptahydrate. This three component mixture has been found to be synergistic in reducing cortisol previously elevated, also the side effects associated with cocktail drug treatment of HIV.

EP 305,902 discloses a mixture of procaine and lidocaine that is injected for the treatment of acquired immunodeficiency syndrome (AIDS). This reference teaches the parenteral administration of an aqueous composition comprising ascorbic acid, procaine HCl and lidocaine HCl. This reference fails to disclose or suggest that the enteral administration would be beneficial in decreasing the adverse side effects associated with anti-HIV drugs such as AZT. This reference also fails to disclose a pharmaceutical composition comprising a cortisol blocker and at least one anti-HIV compound.

U.S. Patent 5,283,258 to Koch discloses a procaine acid addition salt, wherein the acid is attached to diethylamino nitrogen, and is complexed with a biologically active organic acid such as a vitamin acid, an essential unsaturated fatty acid, or an alpha amino acid in stoichiometric ratios of organic acid to procaine addition salt to form a double salt complex wherein the organic acid attaches to the p-amino nitrogen. Koch teaches that such double salt complexes protect the procaine molecule from cholinesterase hydrolysis when orally administered to warm blooded animals. Koch also suggests that the double salt complex is disassociated in the cell, releasing the organic acid and the procaine for cellular repair and regeneration. Koch describes a clinical evaluation of his procaine salts with subjects suffering from rheumatoid arthritis. This patent, however, fails to suggest the use of procaine to reduce the side effects associated with anti-HIV cocktails.

In 1990, Monteleoni et al reported in *Neuroendocrinology*, 1990; 52: pages 243-248, on the activity of brain cortex-derived phosphatidylserine on the neuroendocrine and neurovegetative responses to physical stress. In a double blind design, before starting exercise, each human subject received, intravenously, the brain cortex derived phosphatidylserine or a

placebo. Blood samples were collected before and after the exercise and analyzed for plasma ACTH, cortisol and growth hormone. It was determined that physical stress induced an increase in ACTH, cortisol and growth hormone in the placebo groups while the group receiving phosphatidylserine showed a reduced production of ACTH and cortisol.

5 Dehydroepiandrosterone (DHEA) is a naturally occurring hormone produced by the adrenal gland practically in the same area where cortisol is manufactured. The level of serum DHEA decreases in humans from the age of about 25. Studies in humans have indicated that this hormone has the ability to increase muscle strength, add lean body mass, induce body fat loss, prolong endurance and increase IGF-1. Studies have shown that dosages of DHEA as high as 1.6 gm/day are safe and without side effects. Nestler, et al. in the *Journal of Clinical Endocrinology and Metabolism*, Vol. 66, No. 1 (pages 57-61) reported a DHEA study wherein five men were given a placebo and five men were given 1600 mg/day of DHEA for 28 days in a randomized double blind study. The DHEA group evidenced a mean percent body fat decrease of 31% with no change in weight. DHEA subjects also evidenced a fall in mean serum total cholesterol levels. Morales et al, in the *Journal of Clinical Endocrinology and Metabolism*, Vol. 78, No. 6 (pages 1360-1367), reported on a DHEA study wherein a randomized, placebo-controlled, cross-over trial was conducted. The conclusion of this study was that restoration of DHEA (50 mg per day for 6 months) in age advanced humans induced an increase in bioavailable IGF-1, which, with time, may result in an improvement in anabolic processes and physical/psychological well-being.

DHEA levels have also been found to be low in many disease states and AIDS is among them. A connection between low levels of DHEA and the rapid progression of AIDS has been

reported. It has also been suggested that DHEA levels could be used as a biological marker of AIDS, similar to the manner in which CD₄ cell counts are used as a marker. Recently, DHEA, as an anti-cortisol drug, has received attention of the medical as well as the lay media due to its apparent potential for influencing the process of aging. Representative of the work conducted regarding cortisol and aging are Kerr et al., "Corticosteroid Modulation of Hippocampal Potentials; Increased Effect with Aging", *Science*, 245, 1505-1509 and Sapolsky et al., "Glucocorticoid-Sensitive Hippocampal Neurons are Involved in Terminating the Adrenocortical Stress Response", *Proc. Natl Acad. Sci., USA* 81, 6174-6177. In general, these authors seem to suggest that if it is possible to block the rise of cortisol or to lower elevated cortisol in the elderly, then it should have a very important impact on aging.

A further example of known cortisol blockers is the compound Ipriflavone (7-isopropoxy-isoflavone). Ipriflavone is presently used in dosages of about 600 mgs per day to treat women suffering from osteoporosis. Ipriflavone is known to have an anabolic effect on meat producing domestic animals. Human studies with an administration rate of 20 mg/kg/day of body weight, evidenced an increase in body weight of about 5 pounds (2 kg) in four weeks without an increase in caloric intake. Ipriflavone is also known to increase athletic endurance, suppress the catabolic effect of cortisone and conserve nitrogen in skeletal muscle.

Pregnenalone, a pro-hormone like DHEA, is a substance which the body utilizes to synthesize various hormones that regulate metabolism. Pregnenalone is known as a fat controlling agent and a lean tissue builder. Campbell reported in the *Journal of Endocrinology*, 94(2), 1982, pages 225-242, that exogenous pregnenalone increases the production of the

anabolic steroid aldosterone while not increasing the production of the catabolic steroid corticosterone.

Another cortisol blocker useful in the composition and method of the present invention is known as RU 486. This pharmaceutical product acts by blocking both the progesterone and cortisol receptors. Gatti et al. in 1987 reported that the inhibitory effect of cortisol was partially or totally prevented by RU 486. See Gatti et al., (1987), "Inhibition of Cortisol of Human Natural Killer (NK) Cell Activity", *J. Steroid Biochem. Molec. Biol.*, 26, 49-58. While much attention has been paid to the use of RU 486 in blocking cortisol receptors, the prior art has failed to suggest or disclose the combination of RU 486 with anti-HIV drugs such as nucleoside analogue reverse transcriptase inhibitors, protease inhibitors, non-nucleoside analogues and mixtures thereof in a method to reduce the side effects associated with the administration of anti-HIV drugs or anti-HIV cocktails. The term "HIV cocktails", as discussed above, is used by the medical community to refer to the combination of various anti-HIV drugs to enhance their overall efficacy.

Ketaconazole, a known anti-fungal drug, is also a cortisol blocker useful in the compositions and methods according to the present invention. Ketaconazole has been reported to have anti-cortisol activity based upon its binding to glucocorticoid receptors. Ketaconazole has also been used for the treatment of clinical depression, which is often times associated with high cortisol blood serum levels.

Phenytoin (Dilantin) is presently used as an anti-epilepsy drug, however, anti-cortisol activity has recently been reported. In similar fashion, the drug clonidine has been used in the treatment of hypertension and has also evidenced anti-cortisol ability.

β-hydroxy-β-methylbutyrate (HMB) is another compound known to increase lean-mass gains in weight trainers who consumed at least 3 grams per day. HMB is a leucine metabolite and it has been hypothesized from work in animal models that HMB decreases protein breakdown induced by resistance exercise, resulting in increased muscle mass and function.

5 U.S. Patent 5,348,979 discloses a method of protein sparing, comprising orally or intravenously administering to a human β-hydroxy-β-methylbutyric acid (HMB). The '979 patent also teaches that the HMB can be in the free acid form, its mineral salts, esters or lactose derivatives. More specifically, the '979 patent discloses a method for improving the protein nutrition in elderly humans by administering HMB.

10 U.S. Patents 5,360,613; 5,028,440 and 5,087,472 disclose and claim the administration of HMB to humans and meat producing domestic animals for treating elevated blood levels of low density lipoprotein cholesterol and total cholesterol, for increasing lean tissue development and for use as a feed additive. The teachings of U.S. Patents 5,348,979; 5,360,613; 5,028,440 and 5,087,472 are herein incorporated by reference.

15 U.S Patent 5,804,571 to Schein is directed to a method for the protection of individuals from AZT side effects and toxicity. This patent discloses the enteral administration to a patient undergoing AZT therapy an amount of S-ω(ω-aminoalkylamino) alkyl dihydrogen phosphorothioate. This patent teaches that at least one undesired side effect of the AZT treatment selected from the group consisting of nausea, myalgia, insomnia, headache, anemia and
20 neutropenia is reduced or eliminated. This reference fails to suggest or disclose the use of a cortisol blocker, such as a stabilized procaine hydrochloride, to protect a patient from undergoing the undesirable side effects of anti-HIV drugs.

Disclosure of the Invention

There is disclosed an enteral composition comprising at least one anti-HIV agent and at least one cortisol blocker. There is further disclosed a composition wherein the cortisol blocker
5 is selected from the group consisting of procaine HCl, zinc, zinc salts, zinc heptahydrate, ascorbic acid, lidocaine HCl, phosphatidylserine, DHEA, RU-486 HMB, ketoconazole, pregnenalone, phenytoin, clonidine and Ipriflavone.

There is also disclosed a method for the management of side effects associated with anti-HIV drug therapy, said method comprising the enteral administration to a patient undergoing
10 anti-HIV drug therapy a therapeutically effective amount of at least one cortisol blocker. The side effects of anti-HIV drug therapy that can be managed through the method according to the invention include bone marrow suppression, nausea, myalgia, insomnia, Cushing's like symptoms, anemia, disruption of fat metabolism, elevated triglycerides, elevated cholesterol, insulin intolerance, buffalo humps and protease paunches. Through the method according to the
15 invention the side effects of anti-HIV drug therapy can be reduced or prevented.

There is also disclosed a method to treat the catabolic effects associated with HIV in a human, said method comprising the enteral administration to said human of a therapeutically effective amount of a cortisol blocker.

Detailed Description of the Invention

Conventional treatment of HIV infected patients consist of a combination of two or more anti-HIV drugs (the cocktail), which are designed to attack or destroy the virus. Such drugs include nucleoside analog reverse transcriptase inhibitors such as AZT, DDC, DDI, D₄T and 3TC (Epivir). Protease inhibitors such as saquinavir (Invirase/Fortovase Roche), ritonavir (Norvir, Abbott), indinavir (Crixivan, Merck) and nelfinavir (Viracept, Agouron) are also used to treat HIV infections in patients. Non-nucleoside drugs such as nevirapine (Viramune, Boehringer Ingelheim), delavirdine (Rescriptor, Upjohn) and the like have also been used. New drugs which are about to reach the market may also be combined to form a cocktail. Such new drugs include abacavir (Ziagen, Glaxo Wellcome), efavirenz (Sustiva, Dupont- Merck), adefavir dipivoxil bis-Pom PMEA, (Gilead Sciences), and amprenavir (Vertex Pharmaceuticals). Further, drugs still under clinical investigation that will soon be added to the anti-HIV drugs useful in the present invention include BCH-10652 under development by Bio-Chem Pharmaceuticals, FTC-TBD under development by Triangle Pharmaceuticals, MKC-482/TBD under development by Triangle Pharmaceuticals, PMPA/bis-poc PMPA under development by Gilead and others. All of these drugs can be classified as nucleotide analog reverse transcriptase inhibitors, protease inhibitors or non-nucleoside analogs.

Additional new entrants in the anti-HIV drug category are hydroxiurea (HYDREA) under development by Bristol Meyer Squibb which is a ribonucleotide reductase inhibitor that was previously used as a cancer chemotherapeutic agent, and Pentafuside (Trimeris), a fusion inhibitor, and a new generation of zinc finger inhibitors (**nucleocapsid inhibitors**) While the

results have been acceptable for the cocktail therapy, namely reducing the viral load down to almost undetectable levels, serious side effects have been reported in the use of these anti-HIV drugs. These side effects include Cushingoid type symptoms and fat metabolism irregularities.

One aspect of the present invention is directed to the discovery that anti-HIV drugs cause symptoms that have the appearance of a "high cortisol" factor and that the use of an anti-cortisol drug or a combination of anti-cortisol drugs counteracts the side effects associated with anti-HIV drugs. It is believed that the use of anti-cortisol drugs alone might eventually transform an AIDS patient with a wide range of symptomology into an HIV positive, asymptomatic individual.

The HIV virus depresses the human immune system, leaving the AIDS patient vulnerable to diseases that would otherwise not ordinarily be considered fatal. Consequently, anti-HIV drugs cannot be administered in amounts that further suppress the patient's immune system and resistance to disease. As discussed above, the administration of anti-HIV drugs either alone or in combination have been reported to result in abnormal, disfiguring fat deposits, sometimes referred to as buffalo humps and other physical symptoms similar to Cushings disease. These side effects can be prevented, decreased or alleviated through the use of the present invention which utilizes the co-administration of an anti-HIV drug and at least one cortisol blocker. This invention can be accomplished without significant damage to the beneficial therapeutic effects of the anti-HIV drug. More importantly the method and compositions of this invention can prevent, reduce or suppress the deleterious side effects associated with these anti-HIV drugs.

A preferred cortisol blocker useful in the present invention is a high dose form of procaine HCl that has been stabilized for enteral administration. An especially preferred cortisol blocker formulation is a synergistic combination of three anti-cortisol compounds commercially

marketed by Steroidogenesis Inhibitors International of Las Vegas, Nevada under the Anticort trademark. Anticort™ is a mixture of procaine HCl, zinc heptahydrate and ascorbic acid. These cortisol blockers work synergistically to reduce or prevent the side effects associated with Anti-HIV drug cocktails. The weight ratio of procaine HCl to zinc heptahydrate to ascorbic acid can range from 40:1:2 to 160:1:3. Typical daily dosages for a 60 kg human can range from 200-3,000 mg. As used herein and in the claims the term "procaine HCl" includes those stabilized forms of procaine known to those skilled in the art.

As used herein and in the claims, the term cortisol blocker means any known compound or mixture of compounds that blocks, inhibits, retards or prevents the activity of cortisol in a mammal. There is further disclosed a method for the management of side effects associated with anti-HIV drugs, said process comprising administering to a human in need thereof a composition comprising an anti-HIV drug and at least one cortisol blocker. The weight ratio of anti-HIV drug to cortisol blocker can range from 1:20 to 20:1. More preferably, the weight ratio of anti-HIV drug to cortisol blocker is 1:5 to 5:1. The amount of anti-HIV drug and cortisol blocker composition administered to the human ranges from 0.1 to 10 gms per day. More preferred, the human should consume from 0.5 to 5.0 gms per day. On a weight to weight basis, the human should consume from 0.001 to 0.1 gms per kg of body weight per day of the inventive composition. More specifically, a typical adult human (body weight of 75 kgs) should be administered at least one anti-HIV drug and at least 0.5, more preferably at least 0.8 gms of at least one cortisol blocker.

Oral administration of the cortisol blocker is particularly desirable. By oral administration, there is contemplated preparation of the cortisol blocker in any dosage form

capable of oral administration. Such dosage forms include tablets, capsules, caplets, solutions, sublingual dosage forms, suppositories, nasal sprays and the like. The oral dosage form is administered simultaneously with the anti-HIV drug or anti-HIV drug cocktail from 0-60 minutes, preferably 15 minutes, before the anti-HIV drug is administered to the patient.

5 As an effective amount of the compounds of the present invention, administered orally, there is contemplated any amount which would serve to decrease the side effects or reactions and the toxicity of the anti-HIV drug. For example, a single dosage of between about 200 mg - 2 gm for a typical adult patient is contemplated, with a total dosage of up to 5.0 gms per day is contemplated. A preferred dosage routine is every six hours.

10 The oral dosage forms of the present invention may contain pharmaceutically acceptable inert ingredients. As such inert ingredients there are contemplated pharmaceutical carriers, excipients, fillers, etc. which do not interfere with the activity of the compound. Also, fillers such as clays or siliceous earth may be utilized if desired to adjust the size of the dosage form.

15 Further ingredients such as excipients and carriers may be necessary to impart the desired physical properties of the dosage form. Such physical properties are, for example, release rate, texture and size of the dosage form. Examples of excipients and carriers useful in oral dosages forms are waxes such as beeswax, castor wax, glycowax and carnauba wax, cellulose compounds such as methylcellulose, ethylcellulose, carboxymethylcellulose, cellulose acetate, hydroxypropylcellulose and hydroxypropylmethylcellulose, polyvinyl chloride, polyvinyl
20 pyrrolidone, stearyl alcohol, glycerin monostearate, methacrylate compounds such as polymethacrylate, methyl methacrylate and ethylene glycol dimethacrylate, polyethylene glycol and hydrophilic gums.

Also in accordance with the present invention, there is provided a liquid-based dosage form suitable for the administration of the composition to a patient. The liquid base for this dosage form may be any liquid capable of transporting the composition into the body of a patient without disrupting the activity of the compound or harm the patient. Exemplary of such a liquid is an isotonic solution. The isotonic solution may also contain conventional additives therein such as sugars. These solutions can be used in the preparation of oral compositions.

Thus, the compositions of the present invention may be admixed according to known procedures using known excipients. A therapeutically effective amount of the cortisol blockers of the present invention, there is contemplated any amount which would serve to decrease the side effects and the toxicity of the anti-HIV drug.

In one embodiment of the invention, the cortisol blocker is a mixture of procaine HCl, zinc heptahydrate and ascorbic acid. Irrespective of the anti-HIV or anti-HIV drugs used, the total adult dose of the cortisol blocker(s) should be between 100 mg and 2.0 gm per day, more preferably 500 mg and 1.0 gm per day with 750 mg to 1.0 gm being most preferred. The infant/child dose can typically range from 50-500 mg per day with 50-200 mg per day being preferred.

The present invention also relates to a method for treating the catabolic effects of AIDS through the administration of at least one anti-HIV drug and at least one cortisol blocker.

The composition of the present invention may include other materials such as protein, fats, carbohydrates, vitamins, minerals, sweeteners, flavoring agents and the like. For example, the composition of the present invention, anti-HIV drug plus cortisol blockers, may be combined with known food ingredients or dispersed in a liquid such as orange juice, and consumed orally.

The composition of the present invention may also be in the form of a powder, liquid, tablet, capsule, pill, candy, sublingual dosage form, suppositories, confection, food additive or gel cap. Further, the anti-HIV drug and the cortisol blocker may be administered separately to accomplish the objects of the present invention.

5 Procaine hydrochloride, 2-diethylaminoethyl *p*-aminobenzoate hydrochloride, is also known as Novocain[®], Neocaine, Planocaine, and Ethocaine[®]. Procaine, (β -diethylaminoethyl *p*-aminobenzoate) is one of the oldest and most used of the synthetic local anesthetics, having been developed in 1906. The free ester is an oil, but is isolated and used as the hydrochloride salt. It occurs as an odorless, white crystalline powder that is stable in air, soluble in water and
10 alcohol, but much less soluble in organic solvents. Procaine is most stable at pH 3.6 and becomes less stable as the pH is increased or decreased from this value. The procaine molecule is also subject to oxidative decomposition, but this is not a function of the ester linkage, but of the aromatic amine portion.

As mentioned previously, procaine is an anti-cortisol compound that has the ability to
15 decrease the level of cortisol previously elevated in the blood. Additional compounds having anti-cortisol effects include lidocaine HCl, zinc, zinc salts, zinc heptahydrate, ascorbic acid, dilantin (also referred to as phenytoin), clonidine, phosphatidylserine, DHEA, RU -486, HMB, ketaconazole, pregnenalone and Ipriflavone. Additional cortisol blockers include pantothenic acid, acetylsalicylic acid (aspirin), dimethyl sulphoxide (DMSO), retinol (vitamin A), co-enzyme
20 Q10, acetyl-L-carnitine and ginkgo beloba.

The present invention also contemplates the separate oral administration of the anti-HIV drug and the cortisol blocker. Therefore, dosages of each component can occur separately, provided both components are found systematically in the human.

In order to demonstrate the present invention, the following example is submitted.

EXAMPLE I

Three groups of 10 rats (Control, Control Cortisol Blocker and Control Anti-HIV), each weighing about 200 gms, are fed a standard laboratory diet supplemented as described below, for a period of 60 days. The standard rat diet contains 15% protein, 28% fat and 57% carbohydrate. A fourth group of 10 rats (Experimental) is fed the same standard diet as the Controls, except for the addition of a mixture of procaine HCl, ascorbic acid, zinc heptahydrate and AZT.

The weight ratio of the three part cortisol blocker to AZT is 4:1. The Experimental group diet is a 98 weight % blend of the standard diet with 2 weight % of the cortisol blocker/anti-HIV drug mixture. The Control cortisol blocker diet contains the same amount of procaine HCl as the Experimental. In similar fashion, the Control Anti-HIV diet contains the same level of AZT as the Experimental. Over the 60 day feeding period, energy intake of the Experimental and Control groups is about 250 calories per day.

Data on diet consumption per day is collected and the animals are also weighed daily. On days 7, 21, 39 and 60, post feeding, the rats are evaluated for total body fat using the water tank method as known to those skilled in the art. On day 7 post feeding, each rat is placed in an exercise cage driven by an electric motor. The speed of the exercise cage is set at 100 rpm. The

time for each rat to fail to keep up with the set speed is measured. Failure to meet the set speed of the wheel is determined when the rate becomes inverted within the cage. The time to failure is a measure of endurance of the rat and simulates strenuous exercise in the human thus creating trauma in the rat which induces cortisol production. This procedure of exercise to exhaustion is performed daily except for days 14, 21, 28, 35, 29, 46, 53 and 60.

The exercise cage data will indicate that the average time to exhaustion of the Experimental group is 30% greater than the Control Anti-HIV and about equal to the Control and Control Cortisol Blocker groups. This is evidence that the combined administration of a cortisol blockers and an anti-HIV drug decreases the side effects associated with the administration of anti-HIV drugs to a mammal. The data will also indicate that the Experimental group gained about 15% in body weight over the Control Anti-HIV group, further demonstrating the benefits of the present invention.

In one embodiment of the present invention, there is provided a container or package containing a pharmaceutically acceptable mixture of cortisol blocker and anti-HIV drug in a unit dosage quantity (i.e., pills or capsules). In another embodiment, the composition of this invention is in combination with a liquid or powdered base, such as milk, glucose, protein, flavoring agents or carbohydrates, to improve patient acceptance of the composition.

Example II

To evaluate toxicity to the murine hematopoietic system, an exogenous spleen colony (CFU-S) assay is used. A suitable number of murine bone cells are injected (intravenously) into lethally irradiated syngeneic mice (Ref. Hodgson, G.S., and Bradley, T.R., *Properties of*

Haematopoietic Stem Cells Survive 5-FU Treatment: Evidence for a pre-CFU-S Cell 48, Nature 281:381, 1979).

Colonies are found in the spleen of the recipients on Day 9 or 10; there is a linear relationship between the number of cells injected and the number of spleen colonies. The spleen colonies originate from a single cell, and contain cells of the erythroid, granulocytic and megakaryocytic series.

A mixture of Procaine HCl, ascorbic acid and zinc heptahydrate (dissolved at 4° C. in Lactated Ringer's and 5% Dextrose, pH adjusted to 7.2-7.3 with sodium bicarbonate, immediately prior to use) is administered at 900 mg/kg orally followed within 30 minutes with AZT (dissolved in sterile water prior to use at 20 mgAZT/ml) at 400 mg/kg intraperitoneally.

At 20 hours after drug administration, each mouse is sacrificed and bone marrow is extracted from the femurs into McCoy's 5A medium (GIBCO Grand Island, N.Y.) on ice. Nucleated marrow cells are quantitated, and 5×10^4 cells are injected intravenously into syngeneic recipient mice one hour after they receive 800 rads whole body radiation. Nine days later, the recipient animals are sacrificed, and the spleens are removed and fixed in Boulin's solution. Surface colonies are then counted.

The data will demonstrate that the animals receiving the procaine HCl, ascorbic acid, zinc heptahydrate treatment had a higher CFU-S survival rate than the group that did not receive the inventive synergistic anti-cortisol combination.

Example III

1000 mg of procaine HCl is suspended in an isotonic solution. This suspension is administered to a patient undergoing treatment with a protease inhibitor.

Example IV

1000 mg of procaine HCl is admixed with hydroxypropylcellulose and stearyl alcohol. The mixture is then compressed into tablet form. 200 mg/m² body surface area of procaine HCl thus prepared is administered orally to a patient undergoing treatment with AZT.

5

Example V

700 mg of procaine HCl is admixed with hydroxypropylcellulose and glycowax. The mixture is then compressed into tablet form. 500 mg of procaine thus prepared is administered orally to a patient undergoing treatment with AZT, 25 minutes before administration of AZT.

Example VI

In this experiment a matrix is constructed which varies the dose of cortisol blocker, the mixture of cortisol blockers, the anti-HIV drug, the mixture of anti-HIV drugs and the doses per day. The parameters for each experimental group are set forth in Table I.

Table I

Group	Procaine 200 mg/dose times/day	Zn ¹ 10 mg/dose times/day	Ascorbic Acid 10 mg/dose times/day	AZT times/day	Protease Inhibitor, ritonauir times/day	3TC, Epivir times/day
1	3			3		
2	4			4		
3	6			6		
4	3	3		3		
5	4	4		4		
6	6	6		6		
7	3	3		3		
8	4	4	4	4		
9	6	6	6	6		
10	3			3	3	
11	4			4	4	
12	6			6	6	
13	3	3		3	3	
14	4	4		4	4	
15	6	6		6	6	
16	3	3	3	3	3	
17	4	4	4	4	4	
18	6	6	6	6	6	

Group	Procaine 200 mg/dose times/day	Zn ¹ 10 mg/dose times/day	Ascorbic Acid 10 mg/dose times/day	AZT times/day	Protease Inhibitor, ritonauir times/day	3TC, Epivir times/day
19	3	3	3	3		3
20	4	4	4	4		4
21	6	6	6	6		6
22	3	3	3			
23	4	4	4			
24	6	6	6			
25				3		
26				4		
27				6		
28				3	3	
29				4	4	
30				6	6	
31				3		3
32				4		4
33				6		6

1 - as zinc heptahydrate

The anti-cortisol compound or compounds are administered about 15 minutes prior to the anti-HIV drug or drugs. The data will evidence that Groups 25 - 33 experience bone marrow suppression, nausea, myalgia, insomnia, Cushing's syndrome, anemia, disruption of fat

metabolism, elevated triglycerides, elevated cholesterol, insulin intolerance, buffalo humps and protease pauches. In Groups 1 - 6 the side-effects of anti-HIV drug therapy are somewhat reduced while in Groups 16-24 the above recited side-effects are not present or greatly reduced.

5 **Industrial Applicability**

The medical community is constantly searching for compositions and methods that will alleviate or reduce the side effects associated with the administration of anti-HIV drugs. These side-effects are so profound that tens of thousands of cases have been reported where the patient has interrupted or stopped his/her anti-HIV cocktail therapy. The present invention is based, in part, on the combination of two known chemical entities which reduce the deleterious high cortisol consequences associated with anti-HIV medications. The present invention will be of substantial benefit to all patients that require anti-HIV therapy.

Although the invention has been described in connection with certain specific embodiments, it will be readily apparent to those skilled in the art that various changes can be made to suit specific requirements without departing from the spirit and scope of the invention.

I claim as my invention:

1. A composition for enteral administration comprising at least one anti-HIV drug and at least one cortisol blocker.
2. The composition according to claim 1 wherein said anti-HIV drug is selected from the group consisting of AZT, DDC, DDI, D₄T, 3TC, saquinavir, ritonavir, indinavir, nelfinavir, nevirapine, delavirdine, abacavir, efavirenz, adefavir, BBH-10652, FTC-TBD, NKC-482/TBD, PMPA/Dis-POCPMPA.
3. The composition according to claim 2 wherein said anti-HIV drug comprises of at least two anti-HIV drugs.
4. The composition according to claim 1 wherein said cortisol blocker is selected from the group consisting of procaine HCl, ascorbic acid, zinc, zinc salts, zinc heptahydrate, lidocaine HCl, phosphatidylserine, HMB, DHEA, ketoconazole, pregnenolone, phenytoin, clonidine and Ipriflavone.
5. The composition according to claim 1 wherein said composition is in the form of a powder, liquid, tablet, capsule, pill, suppository, nasal spray, nasal drops, candy or gel cap.
6. A method for the management of side effects associated with the administration of anti-HIV drug therapy, said method comprising the enteral administration to a patient undergoing anti-HIV drug therapy a therapeutically effective amount of at least one cortisol blocker.
7. The method according to claim 6 wherein said anti-HIV drug is selected from the group consisting of AZT, DDC, DDI, D₄T, 3TC, saquinavir, ritonavir, indinavir, nelfinavir,

nevirapine, delevirdine, abacarvir, efavirenz, adefavir, BBH-10652, FTC-TBD, NKC-482/TBD, PMPA/Dis-POCPMPA.

8. The method according to claim 6 wherein said cortisol blocker is selected from the group consisting of procaine HCl, ascorbic acid, zinc, zinc salts, zinc heptahydrate, lidocaine HCl, phosphatidylserine, DHEA, RU-486, HMB, ketoconazole, pregnenalone, phenytoin, clonidine and Ipriflavone.
9. The method according to claim 6 wherein said anti-HIV drug and cortisol blocker are in admixture and are in the form of a powder, liquid, suppository, nasal drops, nasal spray, tablet, capsule, pill, candy or gel cap.
10. A method for the treatment for human immunodeficiency virus infected patients, said method comprising enterally administering to said patient at least one anti-HIV drug and at least one cortisol blocker at levels effective to protect the patient from at least one undesirable side effect of the anti-HIV drug selected from the group consisting of bone marrow suppression, nausea, myalgia, insomnia, Cushings like syndrome, anemia, disruption of metabolism, elevated triglycerides, elevated cholesterol, insulin intolerance, buffalo humps and protease paunches.
11. The method according to claim 10 wherein said anti-HIV drug is selected from the group comprising AZT, DDC, DDI, D₄T, 3TC, saquinavir, ritonavir, indinavir, nelfinavir, nevirapine, delevirdine, abacarvir, efavirenz, adefavir, BBH-10652, FTC-TBD, NKC-482/TBD, PMPA/Dis-POCPMPA.
12. The method according to claim 10 wherein said cortisol blocker is selected from the group consisting of procaine HCl, ascorbic acid, zinc, zinc salts, zinc heptahydrate,

lidocaine HCl, phosphatidylserine, HMB, DHEA, ketaconazole, pregnenalone, penytoin, clonidine and Ipriflavone.

13. The method according to claim 10 wherein said anti-HIV drug comprises at least two anti-HIV drugs.
14. The method according to claim 10 wherein the anti-HIV drug and cortisol blocker are in admixture and are in the form of a powder, tablet, suppository, nasal spary, nasal drop, liquid, capsule, pill or gel cap.
15. A method to treat the catabolic effects associated with human immunodeficiency virus in a human, said method comprising the enteral administration to said human, of a therapeutically effective amount of at least one cortisol blocker.
16. The method according to claim 15 wherein said cortisol blocker is selected from the group consisting of procaine, ascorbic acid, zinc, zinc salts, zinc heptahydrate, lidocaine HCl, phosphatidylserine, DHEA, RU-486, HMB, ketaconazole, pregnenalone, phentoin, clonidine and Ipriflavone.
17. The composition according to claim 1 wherein said cortisol blocker comprises procaine, zinc heptahydrate and ascorbic acid.
18. The method according to claim 6 wherein said cortisol blocker comprises procaine, zinc heptahydrate and ascorbic acid.
19. The method according to claim 10 wherein said cortisol blocker comprises procaine, zinc heptahydrate and ascorbic acid.
20. The method according to claim 15 wherein said cortisol blocker comprises procaine, zinc heptahydrate and ascorbic acid.

ABSTRACT

The present invention is based, in part, upon the discovery that the use of an anti-HIV drug in combination with at least one cortisol blocker such as procaine, reduces the side effects associated with anti-HIV drugs. The invention also relates to a method of treating the high cortisol catabolic effects of diseases such as AIDS in the HIV positive population and those with AIDS related complexes by the administration of a cortisol blocker. The present invention also discloses a composition comprising an anti-HIV drug and a cortisol blocker. More specifically, the present invention relates to a cortisol blocking composition which comprises procaine, ascorbic acid and zinc heptahydrate.

"Express Mail" Number: EL039911232US

Date of Deposit: January 21, 1999

DECLARATION
AND
POWER OF ATTORNEY

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor of the subject matter which is claimed and for which a patent is sought on the invention for COMPOSITION OF ANTI-HIV DRUGS AND ANTI-CORTISOL COMPOUNDS AND METHOD FOR DECREASING THE SIDE EFFECTS OF ANTI-HIV DRUGS IN A HUMAN, the specification of which (check one):

☒ [x] is attached hereto.

☐ [] was filed on _____ as

Application Serial No. _____

and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of the invention claimed in this application, in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

			Priority Claimed	
None				
(Number)	(Country)	(Day/Month/Year Filed)	<input type="checkbox"/> []	<input type="checkbox"/> []
			Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	<input type="checkbox"/> []	<input type="checkbox"/> []
			Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulation, §1.56(a) and (b) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

None
 (Application Serial No.) (Filing Date) (Status)(patented,pending abandoned)

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States Provisional Application listed below:

None
 (Application Serial No.) (Filing Date)

I hereby appoint Donald O. Nickey, Reg. No. 29,092, Roger A. Gilcrest, Reg. No. 31,954, James L. Kwak, Reg. No. 41,133, Jeffrey C. Norris, Reg. No. 42,039, Patricia L. Prior, Reg. No. 33,758, or Jeffrey S. Standley, Reg. No. 34,021, c/o Standley & Gilcrest, 495 Metro Place South, Suite 210, Dublin, Ohio 43017-5315, Telephone No. (614) 792-5555 my attorneys, with full power in each of them, of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. All correspondence should be sent to the attention of **Donald O. Nickey** at the address above

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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